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(54) METHODE DE TRAITEMENT DES ISCHEMIES CEREBRALES ET UTILISATION DE L'ERYTHROPOIETINE OU DE DERIVES DE L'ERYTHROPOIETINE POUR TRAITER LES ISCHEMIES CEREBRALES

(54) METHOD FOR THE TREATMENT OF CEREBRAL ISCHAEMIA AND USE OF ERYTHROPOIETIN OR ERYTHROPOIETIN DERIVATIVES FOR THE TREATMENT OF CEREBRAL ISCHAEMIA

(57)

The invention relates to a method for the treatment of cerebral ischaemia and to an agent for the treatment of cerebral ischaemia, notably in humans, of the kind seen, for example, in stroke patients. Surprisingly it was found that the peripheral administration of erythropoietin to ischaemic cerebral tissue has a marked protective effect. Erythropoietin dramatically reduces the area of permanently damaged cerebral tissue, notably in the penumbra, in comparison to results obtained with conventional measures without administration of erythropoietin.

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(57) Abrégé/Abstract:
The invention relates to a method for the treatment of cerebral ischaemia and to an agent for the treatment of cerebral ischaemia, notably in humans, of the kind seen, for example, in stroke patients. Surprisingly it was found that the peripheral administration of erythropoietin to ischaemic cerebral tissue has a marked protective effect. Erythropoietin dramatically reduces the area of permanently damaged cerebral tissue, notably in the penumbra, in comparison to results obtained with conventional measures without administration of erythropoietin.

Abstract

The present invention relates to a method for the treatment of cerebral ischaemia and a drug for the treatment of cerebral ischaemia in particular in humans, as occurs for example in the case of stroke patients.

It was found surprisingly that peripheral administering of erythropoietin to the cerebral tissue affected by the ischaemia has a distinctly protective effect. Erythropoietin has the effect thereby that the region of the cerebral tissue which is damaged permanently, in particular in the penumbra, is dramatically reduced relative to conventional measures in the case of cerebral ischaemia without erythropoietin administration.

Method for the treatment of cerebral ischaemia and usage of erythropoietin or erythropoietin derivatives for the treatment of cerebral ischaemia

The present invention relates to a method for the treatment of cerebral ischaemia and a drug for the treatment of cerebral ischaemia in mammals, in particular in humans, such as occur for example in the case of stroke patients.

In the case of an ischaemic brain infarction, the damaged regions are divided into the ischaemic core zone and the so-called penumbra which surrounds the core. The size of the ischaemic core plus penumbra determines the extent of the damage after ischaemic insult.

Erythropoietin, also called "EPO" for short, is a glycoprotein which occurs naturally in the body with a molecular weight of 30,000 Dalton (W. Jelkman, "Erythropoietin: Structure, Control of Production, and Function", Physiological Reviews, 1992, Volume 72, Pages 449 to 489). It is an essential growth factor for the production of erythrocytes and was isolated for the first time in 1977.

Erythropoietin has been in frequent clinical use for many years in the case of patients with renal anaemia on kidney dialysis, in order to obtain larger quantities of autologue blood before planned operations and it also hit the newspaper headlines as a blood-doping agent.

Erythropoietin proved itself thereby to be exceedingly well tolerated. The side effects which are relevant are in particular the often therapeutically desired stimulation of the haematopoiesis with polyglobulia and an arterial hypertension which is seldom to be seen. Both effects are to be expected mainly after chronic erythropoietin administering. If necessary, they are relatively easy to remedy by medicinal treatment or by blood-letting.

Intolerance reactions or anaphylactic reactions constitute rarities in the case of erythropoietin.

To date there is no effective therapy for cerebral ischaemia, such as for example for the treatment of stroke patients without operating on the head region of the patient.

In PNAS 1998, Volume 95, No. 8, pages 4635 to 4640, Sakanaka M. et al disclose that the central administering of erythropoietin in animal experiments offers a protective effect on cerebral neurons. Because of the knowledge that the blood brain barrier cannot be surmounted by larger proteins, there results in all tests the administering of erythropoietin directly and centrally into the lateral ventricle. Such directly intraventricular administering of erythropoietin, i.e. direct infusion of erythropoietin into the brain tissue, is however ruled out in humans because of the high risks which are associated with the application /unit/and the maintenance of a temporary ventricle drainage, for example of infections or bleeding.

DelMastro L. et al disclose in Oncologist 1998, 3/5, pages 314-318 that the preventive administering of erythropoietin can prevent anaemia in cancer patients who have been treated with chemotherapy and hence can preventively reduce the risk of such patients with respect to cerebral ischaemia as a result of anaemia caused by chemotherapy. A therapy for an already present cerebral ischaemia, in particular in the case of patients not treated with chemotherapy, is not disclosed therein.

It is thus the object of the present invention to make available a method for the treatment of cerebral ischaemia, a drug for usage in the treatment of cerebral ischaemia and also a means for producing a drug for the treatment of cerebral ischaemia, which can be applied simply and with as few side effects as possible and which is also risk-free.

This object is achieved by the method according to claim 1, the usage in order to produce a drug according to claim 9 and the usage according to claim 17. Advantageous developments of the methods and usages according to the invention are given in the respective dependent claims.

The starting point of the method according to the invention and the usages of erythropoietin according to the invention is that, after an ischaemia has taken place, for example after a stroke, as much as possible of the damaged brain tissue, in particular the penumbra, should be saved as soon as possible. It was found that peripheral administering of erythropoietin has a distinctly protective effect on the cerebral tissue affected by the ischaemia. Erythropoietin has the effect thereby that the region of the damaged cerebral tissue, in particular in the penumbra, is dramatically reduced relative to conventional measures in the case of cerebral ischaemia without erythropoietin administration.

This unexpected tissue-saving effect of peripherally administered erythropoietin in cerebral ischaemia in humans should not be taken for granted since erythropoietin is usually not able to surmount the blood brain barrier as it is known as a larger protein with a molecular weight of approximately 30,000 Dalton. A directly intraventricular administering of erythropoietin, i.e. direct infusion of erythropoietin into the brain tissue, is however ruled out in humans usually because of the risks which are associated with the application/~~unit~~/and the maintenance of a temporary ventricular drainage, such as of infections or bleeding.

It is the contribution of the present invention to detect and make it feasible that, surprisingly for the treatment of a cerebral ischaemia which has occurred, erythropoietin can be given peripherally as a drug directly after the damaging occurrence and then it passes into the damaged brain area and becomes effective.

Peripheral administering of erythropoietin, i.e. on this side of the blood brain barrier, is effected advantageously intramuscularly or vascularly. A directly vascular administering, which as is known advantageously with drugs should generally be effected intravenously, is presented here directly in order to bring erythropoietin in contact with the damaged cerebral tissue in one high dose

within a short period of time i.e. as quickly as possible after the damaging occurrence.

It can thus be assumed therefrom that erythropoietin can surmount the blood brain barrier in the damaged regions directly after damage to the brain tissue by ischaemia. It is therefore possible to administer a drug which contains erythropoietin to the patient who has for example been damaged by a stroke, the erythropoietin actually reaching the damaged brain tissue.

Hence for the first time an effective therapeutic agent is available for cerebral ischaemia in mammals, particularly in humans such as for example in the case of a stroke.

It is furthermore advantageous thereby that the intact blood brain barrier in the non-damaged cerebral tissue regions effectively prevents furthermore penetration of the erythropoietin which is not required there and therefore the tissue regions which are not affected by the ischaemic infarction are not affected by the therapy, i.e. no side effects or only greatly reduced side effects can occur.

Erythropoietin is applied as a drug advantageously with a dosage at an amount of 5,000 to 100,000 units, ideally 35,000 units, per dose, possibly with a daily dose in the first days, for the first time possibly within 8 hours after the stroke. Merely a few doses of erythropoietin suffice thereby to produce the therapeutic effect. Furthermore this has the advantage that the side effects and risks, which are mainly observed in lengthy continuous treatments of other syndromes according to the above-described state of the art, cannot occur or only slightly when using erythropoietin for treating cerebral ischaemia.

Erythropoietin is known from prior art. Human erythropoietin was first isolated from urine (T. Miyake et al 1977, J. Biol. Chem., Volume 252, pages 5558-5564). Today production is effected by DNA recombination. Using this method it can be produced in adequate quantities and be used according to the invention. Further variants of erythropoietin with an altered amino acid

sequence or structure or also fragments with the functional sequence portions which are relevant for the biological function of erythropoietin can be used for the usage according to the invention and should be included in the term "erythropoietin" as is used in this application. Variability of the erythropoietin variants which can be used according to the invention is produced furthermore from modifications in glycosilation of erythropoietin.

Consequently the erythropoietin to be used according to the invention can concern inter alia human erythropoietin, as it occurs naturally, or else erythropoietin products or erythropoietin analogues (in general: erythropoietin variants or derivatives), which have modifications of natural human erythropoietin, such as for example modifications to the sequence such as deletions and substitutions, or else modifications to the carbohydrate compositions. Such erythropoietin products can be produced by different production methods. Such production methods for erythropoietin variants, derivatives or analogues which can be used according to the invention are for example described in the patent applications WO 86/03520, WO 85/02610, WO 90/11354, WO 91/06667, WO 91/09955, WO 93/09222, WO 94/12650, WO 95/31560 and WO 95/05465, the disclosures of which should all hereby be contained in their entirety in the disclosure content in the present patent application by reference hereto and should be included in the present patent application.

In the following, examples of the method according to the invention and the usages according to the invention are given. There are shown:

Fig. 1 the occurrence of erythropoietin in serum and in the cerebrospinal fluid after a stroke, and

Fig. 2 the size of the lesion after cerebral ischaemia.

In Fig. 1A, the average of the serum concentration of four patients with strokes, i.e. whose peripheral concentration of erythropoietin is measured over several days to whom at approximately 8 hours, approximately 24 hours and again

approximately 48 hours after the stroke were given respectively a dose of 35,000 IE human recombinant erythropoietin (preparation "Neorecormon" by the Hoffmann LaRoche AG company) intravenously. It can be detected that the serum concentration achieves its maximum within the first few days and then decreases sharply subsequently.

In Fig. 1B, the concentrations of EPO are represented in six control patients with non-ischaemic neurological illnesses ("neurological disease controls") after infusion of erythropoietin, in two untreated stroke patients ("stroke controls") without infusion of erythropoietin and also in four stroke patients ("EPO patients") after infusion of erythropoietin as in the case of the control patients. There is represented thereby the average of the EPO concentration in the cerebrospinal fluid, as was determined on average 6.4 hours after a first infusion of 35,000 IE human recombinant erythropoietin (preparation "Neorecormon" by the Hoffmann LaRoche AG company). The four stroke patients ("EPO patients") concern the same patients as in Fig. 1A.

Taking into account the logarithmic scale used in the illustration in Fig. 1B it can be directly detected that the concentration of erythropoietin in the cerebrospinal fluid in stroke patients ("EPO patients") is approximately 100 times above that of control patients treated in the same manner ("neurological disease controls") or also the untreated stroke patients ("stroke controls").

It is the contribution of the present invention to recognise that in the case of a cerebral ischaemia the blood brain barrier is permeable for erythropoietin so that in order to treat a cerebral ischaemia directly after the damaging occurrence erythropoietin can pass peripherally as a drug into the damaged brain area and can become effective.

Fig. 2 shows the extent of the lesion after a stroke in the case of a 73 year-old patient. The illustrated pictures were produced by means of magnetic nuclear resonance spectroscopy ("diffusion weighted MRI").

The patient was infused intravenously approximately 8 hours after a stroke with 35,000 IE human recombinant erythropoietin (preparation "Neorecormon" of the Hoffmann LaRoche AG company). Approximately 24 hours and 48 hours after the stroke a further equally large dose of erythropoietin respectively was given.

Fig. 2A shows thereby three section views from underneath during the course of the therapy through the brain of the patient approximately 7 hours after the stroke. The regions damaged by the stroke can be clearly seen offset by their white colouration.

In Fig. 2B, the damaged regions can be detected approximately 3 days after the stroke likewise by their whitish colouration (with a dark centre).

Fig. 2C shows the same section views after 18 days. It can be clearly seen that the result was a marked reduction in the primary lesion. This reduction in the ischaemic infarction area can be ascribed inter alia to treatment with erythropoietin.

Claims

1. Method for the treatment of cerebral ischaemia in mammals, characterised in that erythropoietin is applied peripherally.

2. Method according to the preceding claim, characterised in that the application is effected vascularly.

3. Method according to the preceding claim, characterised in that the application is effected intravenously.

4. Method according to one of the preceding claims, characterised in that the erythropoietin is applied for the treatment of strokes.

5. Method according to one of the preceding claims, characterised in that the erythropoietin is applied at a dosage of 5,000 IE to 100,000 IE per dose and/or per day.

6. Method according to one of the preceding claims, characterised in that the erythropoietin is applied at a dosage of 35,000 IE per dose and/or per day.

7. Method according to one of the preceding claims, characterised in that native or recombinant, human or animal erythropoietin or a derivative thereof is applied as erythropoietin.

8. Method according to one of the preceding claims, characterised in that a human is treated as a mammal.

9. Usage of erythropoietin in order to produce a drug to be applied peripherally for the treatment of cerebral ischaemia in mammals.

10. Usage according to the preceding claim in order to produce a drug to be applied vascularly.

11. Usage according to the preceding claim in order to produce a drug to be applied intravenously.

12. Usage according to one of the claims 9 to 11 in order to produce a drug to be applied peripherally for the treatment of strokes.

13. Usage according to one of the claims 9 to 12 at a dosage of 5,000 IE to 100,000 IE per dose and/or per day.

14. Usage according to one of the claims 9 to 13 at a dosage of 35,000 IE per dose and/or per day.

15. Usage according to one of the claims 9 to 14, characterised in that a native or recombinant, human or animal erythropoietin or a derivative thereof is used as erythropoietin.

16. Usage according to one of the claims 9 to 15, characterised in that the mammal is a human.

17. Usage of erythropoietin as a drug to be applied peripherally for the treatment of cerebral ischaemia in mammals.

18. Usage according to the preceding claim as a drug to be applied vascularly.

19. Usage according to the preceding claim as a drug to be applied intravenously.

20. Usage according to one of the claims 17 to 19 for the treatment of strokes.

21. Usage according to one of the claims 17 to 20 at a dosage of 5,000 IE to 100,000 IE per dose and/or per day.

22. Usage according to one of the claims 17 to 21 at a dosage of 35,000 IE per dose and/or per day.

23. Usage according to one of the claims 17 to 22, characterised in that a native or recombinant, human or animal erythropoietin or a derivative thereof is used as erythropoietin.

24. Usage according to one of the claims 17 to 23, characterised in that the mammal is a human.

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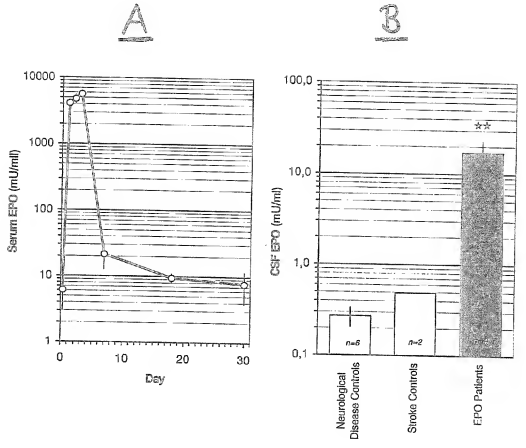
A
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0
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100,0
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CSF EPO (mU/ml)
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n=2
**
Neurological Diseases Controls
Stroke Controls
EPO Patients

Fig. 1

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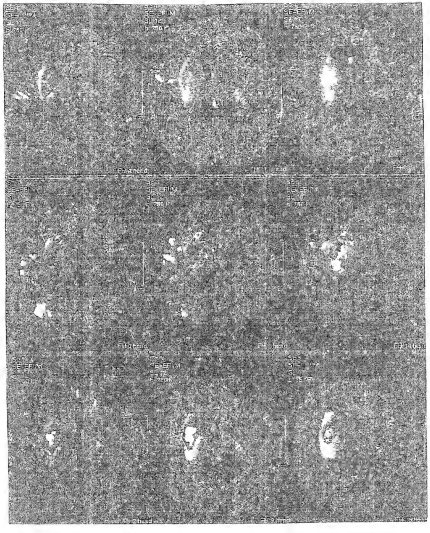

Fig. 2